1130-0108/2014/106/8/522-528
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig (Madrid
Vol. 106, N.º 8, pp. 522-528, 2014

ORIGINAL PAPERS

Insulin resistance and metabolic syndrome are related to non-alcoholic fatty liver disease, but not visceral adiposity index, in severely obese patients

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ABSTRACT

The visceral adiposity index (VAI) is a marker of visceral fat distribution and dysfunction. Visceral adiposity is related to non-alcoholic fatty liver disease (NAFLD); however, there is some controversy regarding the association between VAI and NAFLD. The aim of this study was to analyse the relationship between VAI and NAFLD and to describe the related factors in severely obese patients. A total of 139 patients who underwent bariatric surgery were included in this cross-sectional study. Liver biopsy was performed during surgery. Univariate and multivariate analysis were conducted to study the features related to VAI. A univariate analysis was conducted to identify which factors were associated with liver histology. In the univariate analysis, steatosis, liver inflammation, non-alcoholic steatohepatitis (NASH) and fibrosis were associated with VAI. In the multivariate analysis, only HOMA (Beta: 0.06; $p < 0.01$) and metabolic syndrome (Beta: 1.23; $p < 0.01$) were related to VAI. HOMA, the presence of metabolic syndrome, and waist circumference (WC) were statistically related to the NAFLD activity score (NAS score): HOMA: 0-2: 5.04; 3-4: 7.83; ≥ 5: 11,32; $p < 0.01$; MS: 0-2: 37 %; 3-4: 33.3 %; ≥ 5: 76%; $p < 0.01$; WC: 0-2: 128.7 cm; 3-4: 130.7; ≥ 5: 140.6; $p < 0.01$). For the prediction of NASH (NAS score ≥ 5), the AUROC curve were 0.71 (CI 95 %: 0.63-0.79) for VAI and 0.7 (CI 95 %: 0.62-0.78) for WC. In conclusion, HOMA, WC and metabolic syndrome are related to liver histology in patients with severe obesity. In the multivariate analysis, VAI was associated with HOMA and metabolic syndrome, but not with liver histology.

Key words: Abdominal obesity. Non-alcoholic steatohepatitis. Fatty liver.

Grant information: This study was part of a project funded by the Health Department of Castilla y León (SACYL), Spain (Biomedicine Biotechnology and Health Science Project; PROJECT GRS 401/A/09).

Received: 10-04-2014
Accepted: 22-09-2014

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INTRODUCTION

Obesity is a risk factor for non-alcoholic fatty liver disease (NAFLD). A high body mass index (BMI) and visceral obesity are recognised risk factors for NAFLD. In patients who undergo bariatric surgery, the prevalence of NAFLD exceeds 90 % (1,2). The mean prevalence of non-alcoholic steatohepatitis (NASH) in obese patients is 33 % (3).

Much information has recently been published regarding the role of visceral fat in cardiometabolic disorders and NAFLD. Visceral fat is an active tissue and is able to secrete substances that are involved in inflammation associated with cardiometabolic disorders (4).

An important association between hepatic fat content and visceral adiposity has been reported. Visceral fat is directly linked to the severity of liver inflammation and is a predictive factor of advanced steatohepatitis and fibrosis regardless of insulin resistance (5). Waist circumference (WC) is used as a marker of visceral adiposity; however, it cannot sufficiently discriminate between subcutaneous and visceral fat (6).

The visceral adiposity index (VAI) is a scoring system based on body mass, triglycerides, HDL cholesterol and WC. This index is related to visceral fat distribution and dysfunction and is correlated with cardiovascular risk (7). VAI has been associated with steatosis and necroinflammatory activity in the hepatitis C virus (HCV) genotype 1 (8). Currently, there is some controversy regarding the association between VAI and NAFLD (9,10). No studies

Díez-Rodríguez R, Ballesteros-Pomar MD, Calleja-Fernández A, González-De-Francisco T, González-Herráez L, Calleja-Antolín S, Cano-Rodríguez I, Olcoz-Goñi JL. Insulin resistance and metabolic syndrome are related to non-alcoholic fatty liver disease, but not visceral adiposity index, in severely obese patients. Rev Esp Enferm Dig 2014;106:522-528.

have examined the relationship between this index and NAFLD in severely obese patients. The aim of this study was to analyse the relationship between VAI and NAFLD and to describe their related factors in severely obese patients.

SUBJECTS AND METHODS

Patients

Patients who underwent bariatric surgery at the University Hospital in León (Spain) between June 2008 and October 2011 were prospectively included. The patients were included if they fulfilled the Spanish Society for the Study of Obesity (SEEDO) criteria for bariatric surgery (11): A BMI (body mass index) above 40 kg/m^2 or above 35 kg/m^2 with comorbidities. During surgery (laparoscopic biliopancreatic diversion according to Scopinaro), a liver biopsy was obtained. The exclusion criteria were as follows: Alcohol intake higher than 20 g/day and other causes of liver disease (hepatitis C, hepatitis B, autoimmune liver disease, hemochromatosis or treatment with steatosis-inducing drugs). The study was approved by the Ethics and Clinical Research Committee at our hospital, and written informed consent was obtained from all patients.

Clinical and laboratory data

Clinical and anthropometric data were collected 2-4 weeks before surgery. BMI was calculated using the following equation: Weight (kg)/height (metres)^2. Waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the iliac crest.

The diagnosis of type 2 diabetes was based on the criteria of the American Diabetes Association using a fasting blood glucose value of ≥ 126 mg/dL measured at least twice (12). The diagnosis of high blood pressure (HBP) was based on the following criteria: Systolic blood pressure ≥ 135 mmHg and diastolic blood pressure ≥ 85 mmHg measured three times. Metabolic syndrome was diagnosed according to ATP III criteria (13).

An 8-hour overnight fasting blood sample was obtained to determine the serum levels of alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutaryl transferase (GGT), total cholesterol, HDL-cholesterol (HDL), triglycerides, glucose, insulin, platelets and C-reactive protein (CRP). Insulin resistance (IR) was determined by homeostasis model assessment (HOMA) using the following equation (14): Fasting insulin (μU/ml) x fasting glucose (mmol/L)/22.5). VAI was calculated using the following equations (TG = triglycerides expressed in mmol/L; HDL = HDL-cholesterol expressed in mmol/L) (7):

Males: VAI = (WC/(36.68 + (1.88 x BMI))) x (TG/1.03) x (1.31/HDL)

Females: VAI = (WC/(36.58 + (1.89 x BMI))) x (TG/0.81) x (1.52/HDL)

Histology

Hepatic biopsies were obtained during surgery. A liver biopsy of at least 15 mm was obtained (15) and was analysed by an expert pathologist. The Kleiner classification was used to establish a NAFLD activity score (NAS score) (from 0 to 8), including steatosis (0 to 3), lobular inflammation (0 to 3) and hepatocellular ballooning (0 to 2). The fibrosis stage was classified from 0-4 (16). NASH was considered if the NAS score was ≥ 5.

Statistics

Continuous variables are expressed as the mean (standard deviation), and categorical variables are expressed as frequency and percentage. A p value < 0.05 was considered significant. The statistical analysis was performed with SPSS (Statistical Package for the Social Sciences, version 15 for Windows).

A simple linear regression was performed to identify independent predictors of VAI as a continuous dependent variable. The independent variables included age, gender, BMI, WC, ALT, AST, triglycerides, HDL and total cholesterol, blood glucose, insulin, HOMA score, diabetes, presence of metabolic syndrome, steatosis (grade 0-3), lobular inflammation (grade 0-3), ballooning (grade 0-2), NAS score (not NASH: 0-2, indeterminate: 3-4 and NASH: ≥ 5) and the presence of fibrosis of any grade. The variables that were statistically significant were included in the multivariate analysis (a backward stepwise analysis was carried out). Two multivariate models were utilised according to the histologic features included. In the first model, NAS score components (steatosis, inflammation and ballooning) and fibrosis were included, and in the second model, NAS score and fibrosis were included. HOMA, metabolic syndrome and VAI were excluded from the multivariate analysis to avoid a collinearity problem.

Analysis of variance (ANOVA) or the chi-square test was performed to examine the association between VAI, WC, metabolic syndrome, HOMA, BMI, ALT, AST, HDL, TG, GGT, platelets, CPR and age with liver histology. VAI, WC and HOMA were analysed after being stratified by gender if they were related to NASH (using the NAS score). Patients with any grade of liver fibrosis were grouped for the analysis. A receiver operating characteristic curve analysis was performed to evaluate the ability of VAI or WC to predict NASH (NAS score ≥ 5).

ANOVA was used for quantitative prediction when there were more than two levels in exposure variables. Student's *t*-test was used to compare two mean values; alternatively, the Mann-Whitney *U*-test was used if the mean values did not follow a normal distribution. The chi-square test or Fisher's exact test was used for qualitative prediction. For those ordinal exposure variables a linear trend test was used: ANOVA test for quantitative prediction and chi-square test for qualitative prediction.

RESULTS

In total, 139 patients were included after excluding three patients because liver biopsies could not be obtained during surgery. The patient characteristics and histological features are shown in tables I and II, respectively. Hepatic steatosis was diagnosed in 115 patients (89.9 %) and NASH in 25 (18 %).

Approximately half of the patients (50.4 %) met the criteria for metabolic syndrome: 24.5 % (34/139) had low HDL levels, 35.3 % (49/139) had high triglyceride levels, 100 % had high WC, 49.6 % (69/139) had high blood pressure and 50.4 % (70/139) met the criteria for hyperglycaemia. A total of 76 % (19/25) of NASH patients had metabolic syndrome, and 27.3 % (6/22) of those with normal liver biopsy also had metabolic syndrome.

Factors associated with VAI are shown in table III. In a second multivariate model (in which the only histological liver features included were NAS score and fibrosis), only HOMA (Beta: 0.06; SD: 0.022; p = 0.006) and metabolic syndrome (Beta: 1.234; SD: 0.208; p = 0.000) were related to VAI. The factors related to liver histology are described in table IV.

ALT (UI/L) and AST (UI/L) levels were associated with NAS score (ALT: 0-2: 20; 3-4: 23.7; ≥ 5: 30.7; p = 0.000; AST: 0-2: 25.8; 3-4: 36.4; ≥ 5: 48.4; p < 0.001). HDL (mg/dl) and TG (mg/dl) were also related to NAS score (HDL: 0-2: 52.9; 3-4: 46.63; ≥ 5: 45.7; p = 0.014; TG: 0-2: 123.2; 3-4: 154.7; ≥ 5: 167.76; p = 0.002).

Age, GGT, platelets and CPR levels were not associated with NAS score. For the prediction of NASH, the areas under the receiver operating characteristic (AUROC) curve were 0.71 (95 % CI: 0.63-0.79) for VAI and 0.7 (95 % CI: 0.62-0.78) for WC.

HOMA and WC showed differences based on sex (HOMA: 8.46 for men and 6.2 for women, p = 0.016; WC: 139 for men and 128.4 for women, p = 0.001).

Table I. Characteristics of the included patients

Sex (female)	100 (71.9 %)
Age (years)	43.81 (10.6)
Weight (kg)	125.25 (19.76)
BMI (kg/m^2)	46.83 (6)
DM	34 (24.5 %)
HBP	69 (49.6 %)
Metabolic syndrome	70 (50.4 %)
Waist (cm)	131.37 (14.36)
Glucose (mg/dL)	112.40 (40.35)
Insulin (μU/mL)	24.52 (15)
HOMA	6.89 (4.81)
Total cholesterol (mg/dL)	189 (34.44)
HDL (mg/dL)	49.65 (12.28)
Triglycerides (mg/dL)	139.39 (64.66)
VAI	2.36 (1.36)
AST (UI/L)	22.85 (8.21)
ALT (UI/L)	32.6 (19.5)
GGT (UI/L)	34.24 (23.12)
Platelets (10^3/μL)	24,891.83 (59,647.86)
CRP (mg/L)	8.51 (7.1)

Continuous variables are expressed as the mean (SD), and categorical variables are expressed as frequency (percentage). BMI: Body mass index; DM: Diabetes mellitus; HBP: High blood pressure; HOMA: Homeostasis model assessment; VAI: Visceral adipose index; HDL: HDL-cholesterol; ALT: Alanine transaminase; AST: Aspartate aminotransferase; GGT: Gamma-glutaryl transferase; CRP: C-reactive protein.

Table II. Prevalence of histological abnormalities in liver biopsies

Steatosis	Grade 0	24 (17.3 %)
	Grade 1	60 (43.2 %)
	Grade 2	34 (24.5 %)
	Grade 3	21 (15.1 %)
Inflammation	Grade 0	52 (37.4 %)
	Grade 1	73 (52.5 %)
	Grade 2	11 (7.9 %)
	Grade 3	3 (2.2 %)
Ballooning	Grade 0	87 (62.6 %)
	Grade 1	40 (28.8 %)
	Grade 2	12 (8.6 %)
NAS score	0-2	78 (56.1 %)
	3-4	36 (25.9 %)
	≥ 5	25 (18 %)
Fibrosis	Grade 0	119 (85.6 %)
	Grade 1	14 (10.1 %)
	Grade 2	1 (0.7 %)
	Grade 3	3 (2.2 %)
Normal liver biopsy	22 (15.8 %)	

Table III. Univariate and multivariate analysis of the factors associated with VAI

		Univariate			*Multivariate*		
		Beta	*SD*	*p value*	*Beta*	*SD*	*p value*
Age		0.006	0.011	0.563			
Sex (female)		-0.34	0.256	0.186			
BMI		-0.035	0.019	0.069			
Waist		0.017	0.008	0.036	-		
ALT		0.050	0.012	0.000	NS		
AST		0.022	0.006	0.000	NS		
GGT		0.016	0.005	0.001	NS		
Platelets		$1.86x10^{-6}$	0.000	0.340			
C-reactive protein		0.006	0.016	0.707			
Total cholesterol		0.004	0.003	0.228			
HDL-C		-0.066	0.008	0.000	-		
Triglycerides		0.019	0.000	0.000	-		
Glucose		0.014	0.003	0.000	-		
Insulin		0.025	0.007	0.001	-		
HOMA		0.11	0.022	0.000	0.06	0.022	0.006
HBP		-0.005	0.004	0.213	-		
DM		0.636	0.364	0.017	-		
Metabolic syndrome		1.456	0.195	0.000	1.234	0.208	0.000
Steatosis	Grade 0	Reference					
	Grade 1	0.532	0.315	0.094	NS		
	Grade 2	0.709	0.348	0.044	NS		
	Grade 3	1.455	0.390	0.000	NS		
Ballooning	Grade 0	Reference					
	Grade 1	0.482	0.256	0.062	NS		
	Grade 2	0.737	0.413	0.077	NS		
Inflammation	Grade 0	Reference					
	Grade 1	0.469	0.234	0.036	NS		
	Grade 2	1.354	0.428	0.002	NS		
	Grade 3	2.32	0.766	0.003	NS		
Fibrosis	0 *vs.* 1-2-3	1.225	0.329	0.000	NS		
NAS score	0-2	Reference					
	3-4	0.673	0.261	0.011			
	≥ 5	1.11	0.297	0.000			

In the multivariate model shown, the histological features included were NAS score components and the presence of fibrosis. NS: Not significant; BMI: Body mass index; DM: Diabetes mellitus; HBP: High blood pressure; HOMA: Homeostasis model assessment; VAI: Visceral adipose index; HDL: HDL-cholesterol; CRP: C-reactive protein; SD: Standard deviation.

The NAS score was unaffected by sex (females: NAS 0-2: 58 (58 %); NAS 3-4: 25 (25 %); NAS ≥ 5: 17 (17 %); males: NAS 0-2: 20 (51.3 %); NAS 3-4: 11 (28.2 %); NAS ≥ 5: 8 (20.5 %); p = 0.767). BMI and metabolic syndrome showed no differences when stratified by sex. Among men, the NAS score was only related to HOMA (0-2: 5.67; 3-4: 10.54; ≥ 5: 12.56; p = 0.001) and WC (cm) (0-2: 134; 3-4: 138.9; ≥ 5: 151.62, p = 0.001). Among women, HOMA, WC (cm) and VAI were related to NAS score (HOMA: 0-2: 4.82; 3-4: 6.64; NAS ≥ 5: 10.7; p < 0.001; WC: 0-2: 126.8; 3-4: 127; ≥ 5: 135.5; p = 0.024; VAI: 0-2: 1.92; 3-4: 2.54; ≥ 5: 3.01; p = 0.005).

Table IV. Analysis of factors related to liver histology

	VAI	*HOMA*	*Metabolic SD*	*Waist*	*BMI*
Steatosis					
Grade 0 (n = 24)	1.736 (1.22)	3.62 (1.59)	5 (20.83 %)	127.45 (11.55)	45.52 (4.57)
Grade 1 (n = 60)	2.268 (1.37)	5.93 (3.54)	24 (40 %)	128.68 (1.62)	47.14 (6.52)
Grade 2 (n = 34)	2.45 (1.22)	7.27 (4.81)	23 (67.65 %)	134.03 (14.22)	47.57 (6.02)
Grade 3 (n = 21)	3.19 (1.33)	12.7 (5.44)	18 (85.71 %)	139.24 (18.78)	46.20 (5.93)
p value	*0.003**	*0.000**	*0.000**	*0.009**	*0.565*
Inflammation					
Grade 0 (n = 52)	1.94 (1.18)	4.92 (3.2)	16 (30.77 %)	128.71 (12.12)	46.35 (5.53)
Grade 1 (n = 73)	2.43 (1.36)	7.6 (4.9)	42 (57.53 %)	131.49 (13.33)	47.31 (6.57)
Grade 2 (n = 11)	3.29 (1.39)	10.53 (6.56)	9 (81.81 %)	143.36 (24.37)	46.63 (4.51)
Grade 3 (n = 3)	4.26 (0.71)	10.35 (6.53)	3 (100 %)	130.67 (11.50)	43.97 (3.94)
p value	*0.001**	*0.000**	*0.000**	*0.022*	*0.689*
Ballooning					
Grade 0 (n = 87)	2.16 (1.35)	5.26 (3.16)	34 (48.6 %)	128.8 (12.79)	46.19 (6.13)
Grade 1 (n = 40)	2.64 (1.38)	9.16 (5.82)	27 (67.5 %)	133.2 (11.77)	47.73 (5.18)
Grade 2 (n = 12)	2.89 (1.16)	11.15 (5.7)	9 (75 %)	143.92 (24.09)	48.39 (6.37)
p value	*0.064*	*0.000**	*0.002**	*0.001**	*0.262*
NAS score					
0-2 (n = 78)	1.99 (1.21)	5.04 (3.07)	26 (33.3 %)	128.71 (12.07)	46.19 (5.74)
3-4 (n = 36)	2.66 (1.46)	7.83 (4.59)	25 (69.4 %)	130.69 (13.72)	48.37 (6.79)
≥ 5 (n = 25)	3.09 (1.27)	11.32 (6.24)	19 (76 %)	140.64 (18.18)	46.58 (5.36)
p value	*0.000**	*0.000**	*0.000**	*0.001**	*0.192*
Fibrosis					
No (n = 119)	2.212 (1.28)	6.2 (4.47)	54 (45.38 %)	130.42 (20.15)	46.92 (6.07)
Yes (n = 18)	3.43 (1.42)	11.68 (4.54)	15 (85.33 %)	136.47 (13.26)	45.88 (4.93)
p value	*0.001*	*0.000*	*0.000*	*0.291*	*0.52*
Normal liver biopsy					
No (n = 117)	2.45 (1.37)	7.48 (4.97)	64 (54.7 %)	130 (14.14)	47.09 (6.16)
Yes (n = 22)	1.87 (1.22)	3.72 (1.74)	6 (27.27 %)	131.63 (14.45)	45.42 (4.88)
p value	*0.032*	*0.000*	*0.000*	*0.286*	*0.396*

The p-value expressed in the table corresponded to: Analysis of the variance for continuous predictors (expressed as the mean (SD)), Chi-square test for categorical variables (expressed as frequency (percentage)). *Statistically significant linear test (p-value < 0.05). VAI: Visceral adiposity index; HOMA: Homeostasis model assessment; BMI: Body mass index.

DISCUSSION

This is the first cross-sectional study in which the relationship between VAI and liver histology in severely obese patients was analysed. Our data show that IR, WC and metabolic syndrome are related to liver histology in morbid obesity. In the multivariate analysis, VAI was only associated with HOMA and with metabolic syndrome but not with liver histology. In this study, VAI and WC had similar predictive ability for NASH.

This was a cross-sectional study, and the results should be interpreted with caution due to the non-controlled design. This is the main limitation of the study. WC was used as a marker of visceral adiposity; however, it cannot be used to properly discriminate between visceral and subcutaneous fat (17), and it has a different distribution by gender. In this study, visceral fat was not

measured with any imaging methods (due to the high BMI, magnetic resonance or computerised axial tomography was not possible in most patients); thus, it was assumed that VAI and WC are good methods for measuring visceral fat in morbid obesity. This is another limitation of the study.

A low prevalence of NASH and advanced fibrosis were observed in our cohort. The prevalence of NASH in the obese population ranged from 10-56 % (3). In a morbidly obese cohort (18), the prevalence of NASH was 33 % and the prevalence of advanced fibrosis was 10 %. The differences could be due to the proportion of women and the prevalence of DM observed in our series. As in other studies published the liver histology were associated with WC, HOMA, metabolic syndrome (3,10), however this relationship should be interpreted with caution because of the histology prevalence data.

Fibrosis is independently associated with IR and lobular inflammation, and these two factors are related to fibrosis progression in patients with NASH (19,20). Petta et al. found that VAI is associated with fibrosis (approximately 25 % of the cohort had stage 3-4 fibrosis), and van der Poorten et al. suggested that visceral adipose tissue is related to the severity of fibrosis (5). Our data showed that fibrosis is related to IR and VAI; however, due to the low prevalence of fibrosis in our population, these data should be interpreted with caution.

In a controlled study, Vongsuvanh et al. (10) showed that VAI is not associated with steatosis, inflammation or fibrosis. Petta et al. (9) observed that VAI is related to hepatic fibrosis in patients with NAFLD. In the Petta study, the mean BMI was 30, and in the Vongsuvanh cohort, the mean BMIs were 26.9, 30.3 and 31.2 kg/m^2 in the control, steatosis and NASH patients, respectively. In the original cohort (315 patients) selected by Amato (7), the patients had BMIs between 20 and 30 kg/m^2.

The VAI formula includes BMI and WC values. In our cohort of morbidly obese patients, all patients had high BMI and WC values, and due to the design of the formula, those high values most likely compensate for each other. The multiplicative factors of the formula (HDL and triglyceride levels) were distributed similarly in the Petta cohort (9) and in our series, being similar to the data from the original cohort (7) (the prevalence of hypertriglyceridemia was 13 %, and 25 % of the patients showed lower levels of HDL). In the Vongsuvanh series (10), 40 % of the patients showed hypertriglyceridemia according to the ATP III criteria. Unlike what was observed in the Vongsuvanh study, in our cohort, all components of the VAI formula except BMI were associated with the NAS score in the univariate analysis (Table III). But VAI was not related to NAS score in the multivariate analysis. The low prevalence of NASH could explain the difficulty to achieve statistical significance.

Amato et al. have recently indicated that the formula has limited use in patients with high levels of TG or those who are morbidly obese (21). The application of this formula to another population with distinctive baseline characteristics must be performed carefully.

In conclusion, the main factors associated with VAI score were HOMA and metabolic syndrome in severely obese patients. Visceral adiposity (measured by VAI and WC), insulin resistance (measured by HOMA) and metabolic syndrome were related to steatosis, liver inflammation, NASH and fibrosis (WC was not associated with fibrosis) in morbidly obese patients. It is clear that visceral adiposity, metabolic syndrome and NAFLD are interconnected; however, further research is needed to determine the relationship between these factors in morbidly obese patients.

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